#8

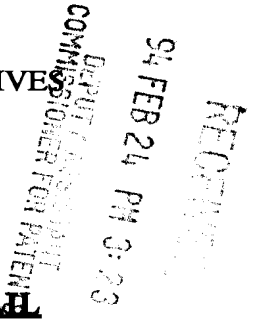
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,535,186

Issued: August 13, 1985

To: G.E. Morris Husbands, John P. Yardley and Eric A. Muth

For: 2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES



BOX PATENT EXTENSION
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

CERTIFICATE OF MAILING BY EXPRESS MAIL UNDER 37 CFR 1.10

"Express Mail" Label Number TB254982893 US

Date of Deposit February 2, 1994

I hereby certify that the following attached papers:

1) Letter of Transmittal of Application for Extension of Patent Term and Depost Account charge order;

2) Application for Extension of Patent Term Under 35 USC 156 including Declaration and 3 Exhibits, plus duplicates of all papers, certified as such;

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to Box Patent Extension, Commissioner of Patents and Trademarks, Washington, DC, 20231.

Roxanne L. Kelly
(Typed or printed name of person mailing paper or fee)

Roxanne L. Kelly
(Signature of person mailing paper or fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,535,186

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To: G.E. Morris Husbands, John P. Yardley and Eric A. Muth

For: 2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES

BOX PATENT EXTENSION
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Re: Deposit Account: 01-1425
American Home Products Corporation
U. S. Patent No. 4,535,186

Sir:

Transmitted herewith is an application for extension of patent term of U.S. Patent No. 4,535,186 in accordance with 35 USC 156 and a duplicate of the papers thereof, certified as such.

Please charge Deposit Account No. 01-1425 in the amount of $1000.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Account No. 01-1425. Two additional copies of this sheet are enclosed.

Respectfully submitted,

Richard K. Jackson
Attorney for Applicants
Reg. No. 24,348

Dated: February 2, 1994

Telephone: (610) 971-2633

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,535,186

Granted: August 13, 1985

Title: 2-Phenyl-2-(1-Hydroxycycloalkyl or 1-Hydroxy-cycloalk-2-enyl)Ethylamine Derivatives

Assignee: American Home Products Corporation

Recorded: May 10, 1984 at Reel 4254 / Frame 0655

BOX PATENT EXTENSION
Honorable Commissioner of
Patents and Trademarks
Washington, D. C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM
35 USC 156

Sir:

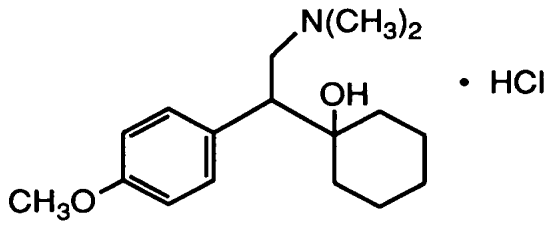
An extension of the patent term of U. S. Patent Number 4,535,186 is requested, based upon the following facts:

(1) The chemical name of the active ingredient of the approved product is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol in the form of its hydrochloride salt.

The generic name of that compound is venlafaxine hydrochloride.

The commercial name of the approved product is EFFEXOR®.

The structural formula of venlafaxine hydrochloride is:



The empirical formula for venlafaxine hydrochloride is: $C_{17}H_{28}NO_2Cl$.

(2) The Federal statute including the applicable provision of law under which the regulatory review occurred is Section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S. Sec. 301 et seq.

(3) The product received permission for commercial marketing on December 28, 1993.

(4) The active ingredient in EFFEXOR®, 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol as its hydrochloride, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for submission pursuant to 35 USC §1.720(f), which sixty day period will expire February 26, 1994.

(6) The patent for which an extension is herewith being sought was granted to:

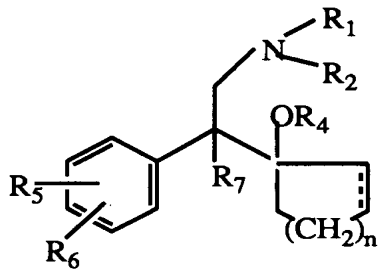
G. E. Morris Husbands, John P. Yardley and Eric A. Muth as Patent Number 4,535,186 on Aug.13, 1985, which patent will expire August 13, 2002.

(7) A copy of the patent for which this extension is sought is attached as Exhibit I.

(8) A copy of the maintenance fee payments made for US Patent Number 4,535,186 are attached as Exhibit II. No disclaimer, certificate of correction or reexamination certificate have been sought or issued.

(9) Claims 1, 2, 3 and 4 of US Patent Number 4,535,186 claim the approved product. As follows, the claims are underlined in a manner showing the relevant claim portions covering the active ingredient of EFFEXOR®.

A compound of the formula:



wherein

the dotted line represents optional olefinic unsaturation, and

R1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R2 is alkyl of 1 to 6 carbon atoms;

R4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R5 and R6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, or trifluoromethyl;

R7 is hydrogen or alkyl of 1 to 6 carbon atoms;

and n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

- 2 -

A compound of claim 1 in which in which R_1 is hydrogen or alkyl of 1 to 3 carbon atoms; R_2 is alkyl of 1 to 3 carbon atoms; R_5 is hydrogen, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms; R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trigluoromethyl or alkanoyloxy of 2 to 3 carbon atoms; R_7 is hydrogen or alkyl of 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof.

- 3 -

A compound of claim 2 in which R_5 and R_6 arein meta or para positions and n is 2. (In this situation, R_5 is hydrogen in meta position and R_6 is methoxy in para position).

- 4 -

The compound of claim 1 which is 1-[(2-dimethylamino)-1-(4-methoxy-phenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

(10)(i) The dates and information necessary for the Secretary of HHS to determine the applicable regulatory review period under 35 USC 156(g) can be determined from the following facts:

a) The Investigational New Drug Application (IND) for venlafaxine hydrochloride was submitted to the Food and Drug Agency (FDA) on October 22, 1985.

b) Receipt of the IND by the FDA was acknowledged on October 24, 1985 and IND number 27,323 was assigned the application. Hence the effective date for IND 27,323 is November 23, 1985, 30 days after receipt of the IND.

c) The New Drug Application (NDA) for venlafaxine hydrochloride was submitted to the FDA on April 25, 1991.

d) Receipt of the NDA by the FDA was acknowledged on June 18, 1991 and NDA number 20-151 was assigned the application.

e) The NDA for EFFEXOR® (venlafaxine hydrochloride) was finally approved on December 28, 1993.

(11) To briefly describe applicant's activities with respect to venlafaxine hydrochloride during the applicable regulatory review period, Exhibit III is attached, to provide an abbreviated list of the most significant correspondence with the FDA from October 22, 1985 to the present time.

(12) It is Applicant's opinion that US Patent Number 4,535,186 is eligible for an extension of a period of 5 years, based upon the following calculation:

a) One half of the IND time from November 23, 1985 to June 18, 1991 (5 years, 6 months, 25 days) is 2 years, 9 months, 12.5 days (1016.5 days).

b) All the NDA time from June 18,1991 to approval on December 28, 1993 is 2 years, 6 months, 10 days (924 days).

c) Total: 5 years, 3 months 22.5 days (1940.5 days).

Hence, under 35 USC 156(g)(6)(A), the patent is entitled to a 5 year extension period.

(13) Applicant acknowledges the duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The $1,000.00 fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account as authorized in the attached transmittal letter, which is submitted in triplicate.

(15) Inquiries relating to this application for patent term extension may be directed to Richard K. Jackson, at telephone number (610) 971-2633. All written correspondence should be addressed to Ronald W. Alice, American Home Products Corporation, Five Giralda Farms, Madison, New Jersey, 07940-0874.

(16) A certified duplicate of these application papers accompanies this application.

(17) The required oath is attached hereto.

Respectfully submitted,

Richard K. Jackson
Attorney for Applicant
Reg. No. 24,348

Dated: February 2, 1994

Telephone: (610) 971-2633

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 USC 156 including its attachments and supporting papers is a duplicate of the original application being currently submitted.

Richard K. Jackson
Attorney for Applicant
Reg. No. 24,348

Dated: February 2, 1994

Telephone: (610) 971-2633

AHP-8162-2-C2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,535,186

Granted: August 13, 1985

Title: 2-Phenyl-2-(1-Hydroxycycloalkyl or 1-Hydroxy-cycloalk-2-enyl)Ethylamine Derivatives

Assignee: American Home Products Corporation

Recorded: May 10, 1984 at Reel 4254 / Frame 0655

BOX PATENT EXTENSION
Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

DECLARATION UNDER RULE 740(a)(17)

Sir:

I, Richard K. Jackson, am a Patent Attorney authorized to practice before the USPTO, presently employed by American Home Products Corporation, with general authority to act in patent matters;

(1) THAT, I have reviewed and understand the contents of the application being submitted pursuant to 35 USC 156, and 37 CFR 1.710;

(2) THAT, I believe the patent is subject to extension pursuant to 37 CFR 1.710;

(3) THAT, I believe an extension of the length claimed is justified under 35 USC 156 and the applicable regulations;

(4) THAT, I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 CFR 1.710;

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

FURTHER, declarant sayeth not.

Date: February 2, 1994

Richard K. Jackson
Attorney for Applicant
Reg. No. 24,348

AHP-8162-2-C2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 4,535,186

Issued: August 13, 1985

To: G.E. Morris Husbands, John P. Yardley and Eric A. Muth

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American Home Products Corporation
U. S. Patent No. 4,535,186

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Respectfully submitted,

Richard K. Jackson
Attorney for Applicants
Reg. No. 24,348

Dated: February 2, 1994

Telephone: (610) 971-2633

EXHIBIT I

United States Patent [19]

Husbands et al.

[11] **Patent Number: 4,535,186**

[45] **Date of Patent: Aug. 13, 1985**

[54] **2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES**

[75] Inventors: **G. E. Morris Husbands**, Berwyn; **John P. Yardley**, Gulph Mills; **Eric A. Muth**, West Chester, all of Pa.

[73] Assignee: **American Home Products Corporation**, New York, N.Y.

[21] Appl. No.: **545,701**

[22] Filed: **Oct. 26, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 486,594, Apr. 19, 1983, abandoned, which is a continuation-in-part of Ser. No. 449,032, Dec. 13, 1982, abandoned.

[51] **Int. Cl.**[3] **C07C 87/28**

[52] **U.S. Cl.** ..... **564/336**; 560/140; 560/250; 560/251; 560/252; 564/157; 564/219; 564/220; 549/443; 549/444; 549/440; 260/465 E

[58] **Field of Search** ..... 564/336, 157, 219, 220; 260/465 E; 560/250, 251, 252, 140; 549/443, 444

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,132,179	5/1964	Clarke	564/355
3,758,527	9/1973	Marxer	560/250
3,847,950	11/1974	Suh et al.	260/340.5 R
3,928,626	12/1975	Yardley et al.	424/330
3,974,157	8/1976	Shetty et al.	260/247.2 B
3,979,444	9/1976	Lednicer	560/250
4,269,788	5/1981	Muller	564/305

FOREIGN PATENT DOCUMENTS

0737473	6/1966	Canada	564/305
1124485	3/1962	Fed. Rep. of Germany .	
6408M	10/1968	France .	

OTHER PUBLICATIONS

Maillard et al., Bull. Soc. Chim. France (1976), No. 6, pp. 2110–2116.

Kvam, Clinical Therapeutics, 2 Suppl. B (1979), pp. 1–12.

Mutak et al., Acta Pharm. Jugosl., 31, 17–26 (1981).

Mutak et al., ibid, 31, 143–150 (1981).

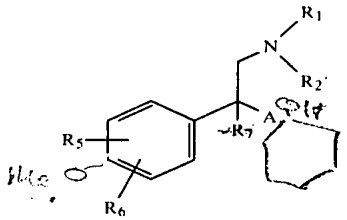
Rajsner et al., Coll. Czech. Chem. Comm., 28, 1031–1043 (1963).

Primary Examiner—Nicky Chan

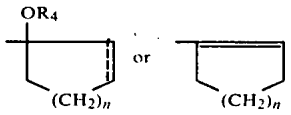
Attorney, Agent, or Firm—Richard K. Jackson

[57] **ABSTRACT**

This invention provides a group of hydroxycycloalkanephenethyl amine antidepressant derivatives of the following structural formula:



in which A is a moiety of the formula



where

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl;

R_2 is alkyl;

R_4 is hydrogen, alkyl, formyl or alkanoyl;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, dialkylamino, alkanamido, halo, trifluoromethyl or, taken together, methylenedioxy;

R_7 is hydrogen or alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

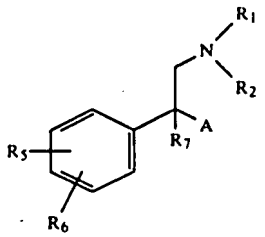
32 Claims, No Drawings

2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES

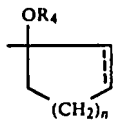
This application is a continuation-in-part of U.S. patent application Ser. No. 486,594, filed Apr. 19, 1983, now abandoned, which application is a continuation-in-part of U.S. patent application Ser. No. 449,032, filed Dec 13, 1982, now abandoned.

DESCRIPTION OF THE INVENTION

In accordance with this invention there is provided a group of substituted phenethylamine derivatives which are central nervous system antidepressants. The compounds of this invention present the following structural formula:

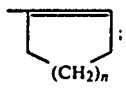


in which A is a moiety of the formula



where

the dotted line represents optional unsaturation, or the analogous cycloalkenyl moiety



R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

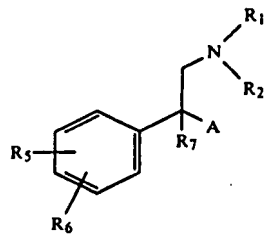
R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula:



in which

A is defined supra;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms.

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which R_5 and R_6 are in meta or para positions and n is 2.

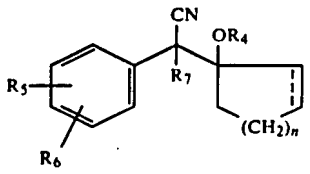
The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms are not nearly as potent as the corresponding free hydroxy bearing derivatives in the test procedures employed and disclosed herein. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed in vivo either via acid hydrolysis in the stomach or enzymatically.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the antidepressant agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo or fluoro substituents.

The compounds of this invention are produced by reaction of a cycloalkanone or a cycloalkenone with an appropriately substituted (ortho or para) phenylacetonitrile anion following the procedure of Sauvetre et al., Tetrahedron, 34, 2135 (1978) followed by reduction (catalytic hydrogenation, borane reducing agents, $LiAlH_4$, etc.) of the nitrile to a primary amine and alkylation of the amine. In the presence of cyclo aliphatic unsaturation, lithium aluminum hydride is the preferred reducing agent. Subsequent acylation of the α-cycloaliphatic hydroxyl group and any phenolic hydroxyl group present may be effected conventionally with a formylating agent such as formyl fluoride or an alkanoic acid halide or anhydride. Symmetrical N-methylation may be accomplished via a modified Eschweiler-Clarks procedure employing a large excess of water as illustrated by Tilford et al., J.A.C.S. 76, 2431 (1954); alternatively the procedure of Borch and Hassid, J. Org. Chem., 37, 1653 (1972) using sodium cyanoborohydride and formaldehyde may be employed. Non-symmetrical

N-alkylation or monoalkylation may be accomplished by stepwise alkylation of the N-trifluoroacetate as illustrated by R. A. W. Johnstone et al., J. Chem. Soc., (C) 2223 (1969). Where R_4 is alkyl it is introduced prior to reduction of the nitrile by conventional O-alkylation.

The intermediate nitriles prepared during the production of the antidepressant agents of this invention represent an additional aspect of the invention. They are depicted by the structural formula:



in which

the dotted line represents optional unsaturation, and

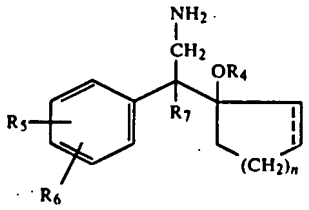
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

The intermediate primary amines produced by reduction of the nitrile depicted in the preceding paragraph represent an additional aspect of the invention. They present the following structural formula:



in which

the dotted line represents optional unsaturation,

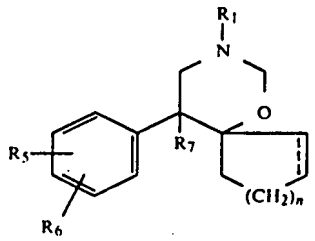
R_4 is hydrogen, or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

Symmetrical N,N-dimethylation may be performed readily by reaction of the primary amino derivative with formaldehyde, formic acid in a large excess of water. An intermediate, 3-aza-1-oxaspiro[5.5]undecane, which represents an additional intermediate of this invention is formed during the reaction and is isolatable. It presents the following structural formula:



in which the dotted line represents optional unsaturation,

R_1 is methyl;

R_5 and R_6 are orthor or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

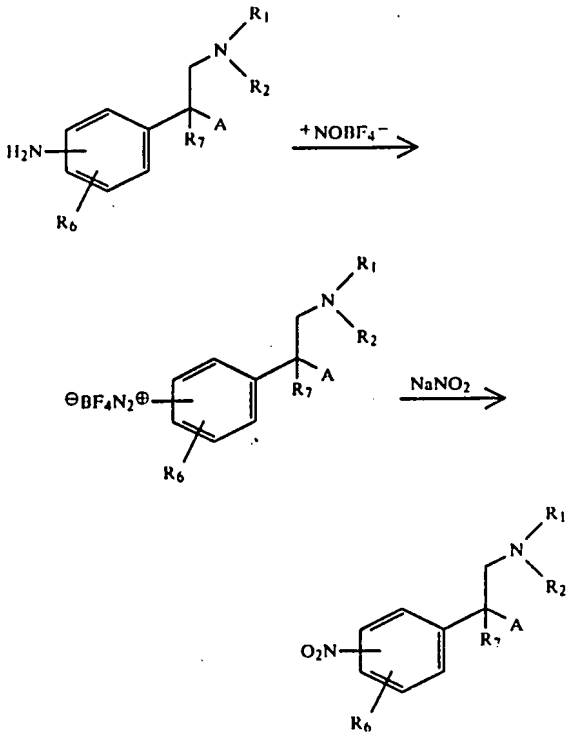
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

These oxaspiro[5.5]undecane intermediates possess similar activity to the corresponding open-ring tertiary amino end compounds of the invention. For example, the oxazine produced in Example 3 is hereinafter compared, in its properties, with the corresponding dimethylamino end compound of Example 3. The end compound is produced from the corresponding oxazine by prolonged reflux in the presence of aqueous formic acid.

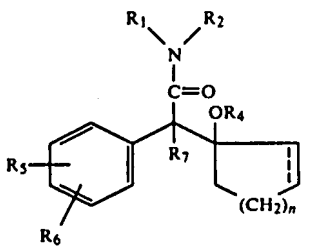
An alternative, and preferred, mode of preparing the compounds of this invention involves the reaction of a cycloalkanone or cycloalkenone with an appropriately substituted phenylacetamide anion following the procedure of Sauvetre et al., ibid., followed by reduction of the amide with lithium aluminum hydride or a borane reducing agent, except in the case of cycloaliphatic unsaturation as discussed, supra, to the corresponding amine. This process is preferred because it is considerably more facile when dealing with meta-substituted or halo-substituted phenylacetamide reactants which pose some problems when proceeding through the acetonitrile intermediate. This route to the desired end products also permits one to readily vary the valued R_1 and R_2 in the initial reactant.

The cyano substituent representing R_5 and/or R_6 is introduced after all reduction steps have been completed by displacement of an R_5–R_6 halo substitution with cuprous cyanide. The amino substituents representing R_5 and/or R_6 are protected throughout the reaction sequence with a protecting group such as 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene which completely blocks the amino nitrogen atom from undesireable reactions. After completion of the reaction sequence, the amino group is deprotected and alkylated or acylated by conventional means to provide a mono- or di-alkylamine or an alkanamido group in each case of 1 to 6 carbon atoms. The nitro substituent representing R_5 and/or R_6 is introduced as an aromatic substituent by diazotization of the aromatic amine followed by treatment with alkali metal nitrite in the presence of copper or by formation of the diazonium tetrafluoroborate and reaction with an alkali metal nitrite, thusly:



The cyano substituent may be introduced via the diazonium salt with cyprous cyanide in analogous manner.

The intermediate amide represents an additional aspect of this invention and is depicted by the following structural formula:



in which

the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

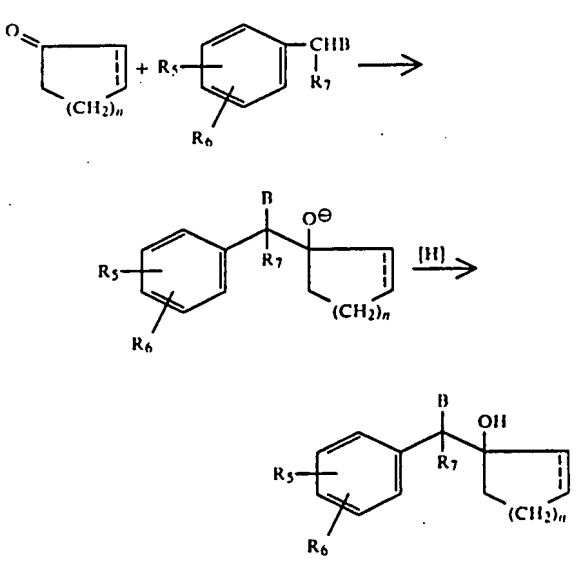
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

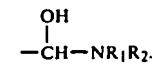
n is one of the integers 0, 1, 2, 3 or 4. When R_4 is alkyl it is introduced prior to reduction. The protecting group employed to prevent reaction at the amino substituent representing R_5 and/or R_6 is any protecting group that will completely prevent reaction at a primary $-NH_2$ substituent, such as 1,2-[bis-dimethylsilylchloride]ethane.

More indirect routes for synthesis of the antidepressant compounds of this invention involve the reaction of a cycloalkenone or a cycloalkenone with an anion of an appropriately substituted phenylacetic acid, salt, ester, aldehyde or alcohol



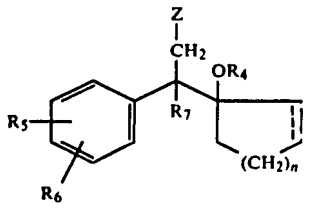
where B represents a carboxyl group or its salt or ester or a —CHO or CH_2OH functional group.

The carboxylic acid group may be converted to an acid halide, active ester or anhydride and directly reacted with the desired amine to yield, after reduction of the resulting amide, the end products of this invention. Also, the carboxylic acid group may be reduced with diisobutyl aluminum hydride or lithium aluminum hydride to obtain the corresponding aldehyde. The ester is readily converted to the aldehyde with diisobutyl aluminum hydride or to the alcohol with lithium aluminum hydride. The aldehyde may be condensed with hydroxylamine to afford the oxime —CH=NOH; with ammonium or a primary amine to afford an imine $-CH=NR_1$ or with a primary or secondary amine to afford

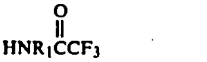


The alcohol $-CH_2OH$ may be converted to the corresponding nitro derivative by producing an organic sulfonate (mesyl ester) or halide followed by displacement with an inorganic nitrite. Reduction of these intermediates yields the primary amine intermediates or the secondary or tertiary amine end products of this invention. The alcohols may be converted to mesylates or tosylates, reacted with KCN to afford the nitrile, converted to the amide and subjected to a Hoffman rearrangement with bromine or chlorine and an alkali metal hydroxide.

Additional routes to the desired products include the reaction of ammonia or HNR_1R_2 with

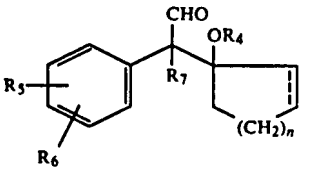


where Z is a leaving group such as a halogen or an organo sulfonyloxy (mesyl, tosyl and the like) group under conventional conditions. If desired, the amine reactant may be initially blocked with a relatively labile acyl group such as trifluoroacetyl to provide a reactant of the formula



prior to reaction with the alkylating reactant employing KOH and a very polar solvent such as dimethylsulfoxide, to provide a tertiary amide from which the acyl group may be readily removed to prepare the compound for non-symmetrical N-alkylation to insert R_2. Rather than N-alkylate, one may acylate or react the secondary amine with an aldehyde and subsequently reduce the amide or Schiff base. Similarly, reaction of the amine with an alkylchloroformate affords, upon reduction, an N-methylated amine. $LiAlH_4$ is a good reducing agent for these processes.

Reductive amination of the aldehyde



with ammonia, a primary amine or a secondary amine (Leuckart reaction) also yields the desired end products.

During the course of the synthesis of the end compounds of the invention by means of processes identified above, any hydroxy group represented by $—OR_4$, R_5 or R_6 may be in the free form or in the form of hydroxy protected by a removable protecting group, except of course, that the hydroxy group is not protected in any case where it is intended to participate in a reaction. The protected form is recommended where the hydroxy group may otherwise undergo an undesired reaction. Examples of protecting groups for hydroxy are given in Protective Groups in Organic Chemistry edited by J. F. W. McOmie, Chapters 3 and 4 (pages 95–182) published by Plenum Press (1973), and Protective Groups in Organic Chemistry by T. W. Greene, Chapters 2 and 3 (pages 10 to 113) published by John Wiley and Sons (1981). The protecting group may be removed at a suitable later stage in the synthesis. Similarly any amino or alkylamino group may be in a protected form where appropriate during the course of the synthesis of the end compounds. Protecting groups for amino are described in Chapter 2 (pages 43 to 94) of the McOmie book and Chapter 7 (pages 218 to 286) of the Greene book.

The end products contain either one or two asymmetric centers depending upon the saturated and unsaturated state of the cycloaliphatic ring, respectively. Individual stereoisomeric forms may be obtained or separated by standard procedures. For instance separation of the mixture in the case of an amine or carboxylic acid may be carried out by neutralisation with a suitable optically active compound to form salts which can be separated. Example 33 illustrates the typical resolution of the product of Example 3, Compound A.

The antidepressant activity of the end compounds of this invention was established by demonstrating that they (1) inhibit ^{3}H-imipramine binding in brain tissue when tested by a method analogous to that of Raisman et. al., Eur. J. Pharmacol. 61, 373–380 (1980); (2) inhibit synaptosomal uptake of norepinephrine (^{3}H-NE) and serotonin (^{14}C-5-HT) following the test procedure of Wood et. al., J. Neurochem. 37, 795–797 (1981); and antagonize reserpine induced hypothermia when tested in accordance with the procedure of Askew, Life Sci. 1, 725–730 (1963).

The results of these procedures affirmed the antidepressant activity of the end compounds of this invention in agreement with the most widely accepted theory of antidepressant activity and in correlation of activity with known tricyclic antidepressants. In at least two instances, namely, with the dimethylamino product of Example 3, and 4-chloro product in Example 11, the undesirable attribute of classical antidepressants observed as an anticholinergic property which is reflected by the inhibition of binding of the muscarinic receptor ligand, 3H-quinuclidinyl benzilate (QNB), and in the inhibition of carbachol-stimulated contraction of the guinea-pig ileum, is missing. Also missing is the attribute of classical antidepressants observed as an antihistaminic property which is reflected by the inhibition of the H_1 histamine receptor ligand, 3H-pyrilamine, and in the inhibition of histamine-stimulated contraction of the guinea-pig ileum.

As representative examples of the activity profile of the end compounds of this invention, the following data for testing of the dimethylamino product of Example 3, hereinafter Compound A, its oxazine variant, hereinafter Compound B, the 4-chloro product of Example 11, hereinafter referred to as Compound C, the 4-bromo product of Example 15, hereinafter referred to as Compound D, the 3-chloro product of Example 17, hereinafter referred to as Compound E, the 3-bromo product of Example 16, hereinafter referred to as Compound F, and the 3,4-dichloro product of Example 19, hereinafter referred to as Compound G, are presented as follows:

Inhibition of ^{3}H-imipramine binding: Compound A (HCl Salt) exhibited an inhibition constant (K_i) vs. ^{3}H-imipramine of 90 nM, making it a fairly potent ligand at this receptor site. Compound B was somewhat less potent, with a K_i of 350 nM. Compound C was virtually equipotent with Compound A, exhibiting a K_i vs. ^{3}H-imipramine of 100 nM. While not as potent as imipramine (K_i=1.7 nM), these values fall in the range of desmethylimipramine (DMI) (K_i=130 nM) and other tricyclic antidepressants. Atypical antidepressants (non-tricyclic) which have been tested, exhibit K_i's greater than 5000 nM in this assay. Compounds D, E, F and G exhibited inhibition constants of 62, 130, 52 and 37, respectively. Compounds A through G, representative of the other compounds of this invention, are thus comparable to known tricyclic antidepressants in this test.

Inhibition of synaptosomal NE and 5-HT uptake: Results of the inhibition of NE and 5-HT synaptosomal uptake, expressed as the inhibitory concentration at which the rate of uptake was reduced to 50 percent (IC_{50}), are presented in the table below, where they are compared with the values for imipramine, DMI and amitriptyline:

Compound	IC_{50} (μM) NE	5-HT
Imipramine	0.26	0.12
DMI	0.15	3.0
Amitriptyline	0.50	0.60
Compound A	0.64	0.21
Compound B	4.7	2.9
Compound C	0.33	0.25
Compound D	0.21	0.11
Compound E	0.16	0.32
Compound F	0.11	0.23
Compound G	0.07	0.08

These results show that Compounds A and C to G are approximately equipotent to imipramine in NE and 5-HT uptake inhibition. Again, Compound B is somewhat less potent.

Inhibition of ^{3}H-QNB binding: In the QNB receptor binding assay, the Compounds A and C-G exhibited an IC_{50} greater than 10^{-5} molar and were therefore essentially inactive. Imipramine and DMI exhibit K_i's of 37 nM and 50 nM, respectively. These results suggest that, unlike the tricyclic antidepressants, Compounds A and C-G would have no muscarinic anticholinergic actions.

Inhibition of Carbachol-stimulated contraction of guinea-pig ileum: While imipramine at 1 μM exhibits a K_B of approximately 100 nM against carbachol-stimulated contraction of the guinea-pig ileum, Compound A was inactive at 1 μM. This result supports the suggestion of a lack of muscarinic anticholinergic action of Compound A.

Inhibition of ^{3}H-pyrilamine binding: While DMI exhibits a K_i versus ^{3}H-pyrilamine binding of 124 nM, Compound A was inactive. Compounds D-G exhibited an IC_{50} greater than 10^{-5} molar. These results suggest that, unlike tricyclic antidepressants, Compounds A and D-G have no antihistaminic property.

Inhibition of histamine-stimulated contraction of the guinea-pig ileum: Imipramine at 1 μM inhibits the histamine-stimulated contraction of the guinea-pig ileum with an approximate K_B of 8 nM. Compound A, in contrast, had no effect in this test at a concentration of 1 μM. This result supports the notion that Compound A has no antihistaminic action.

Antagonism of reserpine-induced hypothermia: The minimum effective dosage (M.E.D.) of compounds A through G established in antagonism of reserpine-induced hypothermia in mice (n=8 per group) in relation to desmethylimipramine (DMI) were:

Compound	Dose, mg/kg, i.p.
DMI	0.4
A	10.0 (and p.o.)
B	30.0
C	10.0
D	3.0
E	1.0
F	1.0
G	3.0

All mice received 5 mg/kg reserpine s.c. 18 h prior to test compound.

DMI, and Compounds A to G, are of approximately equal efficacy in the reversal of reserpine-induced hypothermia. Compound B was less potent than Compound A, Compound C was approximately equipotent with Compound A, Compounds D and G were approximately three times as potent as Compound A, and Compounds E and F were approximately ten times as potent as Compound A in the study.

Hence, the end compounds of this invention are useful in the treatment of depression, for which purpose they may be administered orally or parenterally in an amount sufficient to alleviate the symptoms of depression. The actual amount of antidepressant agent to be used will vary with the severity and nature of the depressed state, the animal being treated and the level of relief sought. In the human, an oral dose of from about 2 to about 50 milligrams, administered as needed represents appropriate posology. Intramuscular administration of from about 1 to about 25 milligrams provides a dosage comparable to that specified for oral administration. As with other antidepressants, therapy should be initiated with lower dosages and increased until the desired symptomatic relief is obtained.

Pharmaceutical compositions containing the antidepressant compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various colouring, flavouring, stabilizing and flavour masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive, provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or

it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 2 mg. or less to 50 mg. or more, according to the particular need and the activity of the active ingredient.

The following examples illustrate the preparative technique employed in production of the compounds of the invention.

EXAMPLE 1

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to −70° C. under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below −50° C. and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below −50° C. for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below −50° C. the temperature was allowed to rise to 0° C. and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. 125°-127° C.).

Mass Spectral Analysis: Molecular weight 245 [(M+1)+ by C.I.M.S.]

N.M.R. Analysis: δ 7.32, 6.95; (4H quartet, p-substituted aromatic) 3.8 (3H singlet, O—CH_3); 3.76 (1H, singlet, CH—CN); 1.56 (10H, multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 2

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium on alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm).

Mass Spectral Analysis: Molecular weight 249 (M+1)+ by C.I.M.S.

Thin Layer Chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

EXAMPLE 3

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)-undecane and
1-[2-dimethyl-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol (12 gm; 0.048 mole) was treated with a mixture of formaldehyde (11 ml), formic acid (14.5 ml, 88%) and water (125 ml) and heated at 100° C. for five hours. The reaction mixture was cooled and extracted with ethyl acetate. This extract was discarded. The aqueous residue was cooled in ice, rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated to an oily residue (8 gm). This mixture of products was chromatographed on 1 kg of Mallinckrodt Silicar CC7 silica gel and the progress of the chromatography was monitored by thin layer chromatography using a system comprising ethanol:2N ammonia:ethyl acetate:cyclohexane 45:8:100:100 (v/v). Fractions containing the desired products were combined and the hydrochloride salts prepared using 4-N-isopropanolic HCl. The yields of the free bases were 1.4 gm (spiro compound) and 4.6 gm (dimethylamine) respectively.

COMPOUND B

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)undecane

Melting Point: 242°-244° C.

Mass Spectral Analysis: Molecular weight 275 (M+1)+ by C.I.M.S.

N.M.R. Analysis: δ 7.22, 6.96 (4H quartet, p-substituted aromatic) 4.78 (2H quartet, O—CH_2—NCH_3) 3.8 (4H, O—CH_3, CH—CH_2—NCH_3) 3.3 (2H, multiplet CH—CH_2—NCH_3) 2.8 (3H, NCH_3) 0.9-1.8 (10H, broad multiplet, aliphatic cyclohexyl)ppm.

Compound A

1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

The hydrochloride: m.p. 215°-217° C.

Mass Spectral Analysis: Molecular weight 279 (M+1)+ by C.I.M.S. (free base).

N.M.R. Analysis: δ 7.32, 6.98 (4H quartet, p-substituted aromatic) 3.78 (3H, O—CH_3) 3.64 (2H, multiplet $CH_2N(CH_3)_2$) 3.06 (1H, multiplet CH—$CH_2(NCH_3)_2$) 2.74 (6H, $N(CH_3)_2$) 1.38 (10H, broad multiplet, alphatic cyclohexyl)ppm.

EXAMPLE 4

1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexene

8.0 grams (0.029 moles) of 1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 300 ml of 2.0N aqueous hydrochloric acid and heated at reflux for 18 hours. It was allowed to cool, neutralized with 15% aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated in vacuo to yield 7.0 grams of solid. This material was converted to the hydrochloride salt by treatment with 5N isopropanolic HCl and recrystallized a second time from isopropanol to yield 2.0 grams of the title compound as a white solid hydrochloride salt, m.p. 187°-189° C.

Analysis for: $C_{17}H_{26}ONCl$: Calculated: C, 69.23; H, 8.91; N, 4.75. Found: C, 69.39; H, 8.95; N, 4.95.

EXAMPLE 5

1-[(α-Aminomethyl)benzyl]-cyclohexanol

Phenylacetonitrile (10 g, 0.08 mole) was added to dry THF (100 ml) and the solution cooled to −70° C. under nitrogen. n-Butyllithium in hexane (64 ml, 0.1 mole) was added dropwise, the temperature being maintained below −40° C. and a yellow precipitate appeared. After addition the reaction mixture was maintained near −70° C. for 30 minutes and cyclohexanone (10 g, 0.1 mole) was added. After a further 45 minutes at −70° C. the temperature was allowed to rise to 0° C. and saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and

evaporated. The product, 1-[α-cyanobenzyl]-cyclohexanol, crystallized (4.93 g, m.p. 100°-102° C.).

Mass Spectral Analysis: Molecular weight 215 (M+).

N.M.R. Analysis: δ 7.4 (5H singlet, aromatic 3.8 (1H, singlet, CH—CN) 1.6 (10H, multiplet aliphatic cyclohexyl)ppm.

A solution of 1-(α-cyanobenzyl)cyclohexanol (3.43 g, 0.02 mole) in a mixture of methanol and ammonia (9:1 v/v, 60 ml) was hydrogenated in a Parr apparatus over 5% rhodium on alumina (2 g). The catalyst was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated. The hydrochloride m.p. 220°-222° (1.2 g) crystallized from diethyl ether-acetone.

Analysis for: $C_{14}H_{21}NO.HCl$: Calculated: C, 64.29; H, 8.67; N, 5.47%. Found: C, 65.74; H, 8.51; N, 5.56%.

N.M.R. Analysis (DMSO) δ 7.73 (5H singlet, aromatic) 3.46 (2H multiplet CH_2—NH_2), 3.0 (1H multiplet CH—CH_2NH_2) 0.9-1.7 (10H multiplet-aliphatic cyclohexyl) ppm.

Mass Spectral Analysis by Chemical Ionization: 220 $(M+H)^+$ (Mol. Wt. 219) (free base).

EXAMPLE 6

1-(α-[(Dimethylamino)methyl]benzyl)-cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.36 g, 0.006 mole) was dissolved in a mixture of formaldehyde (2 ml) formic acid (2.6 ml) and water (25 ml), and refluxed at 95° C. for 18 hours. The reaction mixture was cooled, basified with solid KOH and extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulphate and evaporated. The hydrochloride (m.p. 225°-227° C.) was prepared using 3N-isopropanolic HCl. Yield 589 mg.

Analysis for: $C_{16}H_{25}NO.HCl$: Calculated: C, 67.36; H, 9.12; N, 4.88%. Found: C, 67.7; H, 9.23; N, 4.93%.

Mass Spectral Analysis: Molecular weight 247 (M^+, *free base*).

N.M.R. analysis: (DMSO) δ 7.4 (5H singlet, aromatic), 3.68 (2H, multiplet CH_2—N $(CH_3)_2$, 3.18 (1H, multiplet CH—CH_2N—$(CH_3)_2$ 2.68 (6H, $N(CH_3)_2$; 0.9-1.7 (10H multiplet aliphatic cyclohexyl)ppm.

EXAMPLE 7

1-(α-[(Methylamino)methyl]benzyl)cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanoi (1.59 g., 0.007 (mole) was dissolved in diethyl ether (10 ml.) and cooled to 5° C. Trifluoroacetic anhydride (2 g) was added and the mixture stirred at 0° C. for 30 minutes. The mixture was neutralized using saturated sodium bicarbonate solution and the layers separated. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. A crystalline trifluoroacetamide m.p. 78°-80° C. was obtained (975 mg.).

The trifluoroacetamide (975 mg.) was dissolved in dry acetone (20 ml.) and treated with methyl iodide (2 g.). The solution was warmed to reflux temperature and dry powdered potassium hydroxide (1 g.) added, followed by excess methyl iodide. The mixture was refluxed for five minutes, then cooled and the acetone evaporated. Water (20 ml.) was added and the mixture refluxed for 15 minutes. It was cooled and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and evaporated to a crystalline product m.p. 92°-94° C. This was converted to the hydrochloride using 3N-isopropanolic HCl. Yield 235 mg., m.p. 208°-210° C.

N.M.R. Analysis ($CHCl_3$), δ 7.3 (7H, aromatic, HCl and NH.CH_3); 3.9 (1H multiplet CH—CH_2NH_2); 3.25 (2H multiplet CH_2—NH_2); 2.6 (3H singlet NH—CH_3); 0.8-1.9 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight by chemical ionization/M.S. 233 (M+1 at 234, free base).

EXAMPLE 8

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol acetate

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol, (0.5 g., 0.0025 mole) was treated with acetic anhydride (1 ml.) and pyridine (3 ml.) and the mixture stood at room temperature overnight. The reaction mixture was poured into water, basified with solid KOH and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulphate and evaporated to an oil. After azetropic distillation with toluene to remove traces of pyridine, the oil was treated with 3N isopropanolic HCl and crystalline hydrochloride as the title compound was obtained (70 mg.) m.p. 163°-165° C.

NMR Analysis: ($CHCl_3$) δ 7.35 (5H singlet, aromatic); 4.2 (1H multiplet $CHCH_2N(CH_3)2$; 3.6 (2H multiplet CH_2—$N(CH_3)_2$); 2.65 (6H singlet, $N(CH_3)_2$); 2.1 (3H singlet, —O—C—CH_3): 0.9-1.7 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight 289 (M^+, free base).

EXAMPLE 9

1-[cyano(p-chlorophenyl)methyl]cyclohexanol

By replacing the p-methoxyphenyl acetonitrile in Example 1 by a molar equivalent amount of p-chlorophenyl acetonitrile, there was obtained 1-cyano(p-chlorophenyl)methyl cyclohexanol (13.7 g.) m.p. 115°-117°.

Mass Spectral Analysis: Molecular weight 249 $(M+1)^+$ by C.I.M.S.

EXAMPLE 10

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol

Lithium aluminum hydride (3.5 g.) was suspended in ice cold tetrahydrofuran (125 ml.) and concentrated sulphuric acid (2.5 ml.) added cautiously, with stirring. After one hour, 1-[cyano(p-chlorophenyl)methyl]cyclohexanol (15 g., 0.06 mole) was dissolved in tetrahydrofuran (100 ml.) and added rapidly dropwise with vigorous stirring and cooling. After a further two hours, a tetrahydrofuran-water mixture (1:1; 30 ml.) was added followed by 10% sodium hydroxide solution (50 ml.). The tetrahydrofuran was decanted and the residue washed well with diethyl ether and ethylacetate. The combined organic solution was dried over anhydrous potassium carbonate and evaporated to an oil (12 g.)

Mass Spectral Analysis: Molecular weight 253 $(M+1)^+$ by C.I.M.S.

EXAMPLE 11

1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol (12 g., 0.04 mole) was treated with a mixture of formaldehyde (13.7 ml.) formic acid (18.1 ml.) and water (160

ml.) and refluxed at 100° C. for four hours. The reaction mixture was cooled extracted well with ethyl acetate and the extract discarded. The aqueous residue was cooled in ice and rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated. A crystalline solid (3 g.) was filtered. It was converted to the hydrochloride salt using 4N-isopropanolic HCl; yielding 4.7 g., m.p. 241°-243° C.

Mass Spectral Analysis: Molecular Weight 281 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.35 (4H singlet characteristic of 4chloro substitution) 3.65 (2H multiplet, CH_2—$CHN(CH_3)_2$), 3.0 (1H multiplet $CH_2CHN(CH_3)_2$ 1.4 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 12

1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol

By replacing 1-[α-(aminomethyl)benzyl]cyclohexanol with a molar equivalent amount of 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol in Example 7, 1-[1-(4-methoxyphenyl)-2-methylamino)ethyl]cyclohexanol hydrochloride (m.p. 164°-166° C.) was obtained.

Mass Spectral Analysis: Molecular Weight 263 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.28, 6.92 (4H quartet, p-substituted aromatic) 3.76 (3H singlet, OMe) 3.4 (2H multiplet, CH_2—$CHNCH_3)_2$ 2.9 (1H multiplet, $CH_2CHN(CH_3)_2$) 2.54 (3H, NCH_3) 1.4 (10H broad multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 13

4-bromo-N,N-dimethylbenzene acetamide

Para-bromophenylacetic acid (50 g., 0.233 mole) was dissolved in methylene chloride (500 ml) and treated with oxalyl chloride (23.3 ml., 0.27 mole) and D.M.F. (0.5 ml) at room temperature. The mixture was stirred for four hours until gas evolution ceased. The solvent was evaporated and the residue dried under vacuum to remove excess oxalyl chloride. The residue was dissolved in methylene chloride (300 ml) and treated with an excess of gaseous dimethylamine. The mixture was stirred overnight and the solvent evaporated. The residue was redissolved in methylene chloride and the solution washed with saturated sodium bicarbonate solution, N-hydrochloric acid, water, brine, dried over magnesium sulphate and evaporated. The buff-colored crystals were filtered with hexane and air-dried. Yield 51.2 g., m.p. 73°-76° C.

Analysis for: $C_{10}H_{12}NOBr$: Calculated: C, 49.59; H, 4.96; N, 5.79. Found: C, 48.98; H, 5.14; N, 5.77.

NMR Analysis ($CHCl_3$): δ 7.55 (4H quartet, aromatic) 3.65 (2H singlet) 2.95 (6H singlet, $N(CH_3)_2$)ppm.

EXAMPLE 14

1-[(4-bromophenyl)[(dimethylamino)carbonyl]methyl]-cyclohexanol

4-bromo-N,N-dimethylbenzene acetamide (15 g., 0.06 mole) was added to dry T.H.F. (250 ml) and the solution cooled to −78° C. under nitrogen. Straight chain butyl lithium in hexane (43.3 ml, 0.06 mole) was added dropwise, the temperature being maintained below −70° C. throughout. An orange coloured precipitate formed. After addition, the reaction mixture was maintained near −70° C. for 20 minutes and cyclohexanone (7.5 ml, 0.07 mole) was added. After a further 50 minutes at −78° C. the reaction mixture was poured into stirring saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated. The product crystallised and was filtered with isopropanol (9.8 g., m.p. 140°-144° C.).

Analysis for: $C_{16}H_{22}NO_2Br$: Calculated: C, 56.47; H, 6.47; N, 4.12. Found: C, 57.22; H, 6.66; N, 4.21.

NMR Analysis ($CHCl_3$) δ 7.35 (4H, aromatic) 3.63 (1H singlet CH—$CON(CH_3)_2$) 2.95 (6H singlet, N—$(CH_3)_2$); 1.45 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 15

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol

Lithium aluminum hydride (0.7 g.) was suspended in dry THF (25 ml) cooled to 0° C. and concentrated sulfuric acid (0.5 ml) cautiously added in an in situ preparation of aluminum hydride. The mixture was stirred for one hour at 0° C. and the amide, 1-[(4-bromophenyl)[dimethylaminocarbonyl]methyl]cyclohexanol (4 g., 0.012 mole) was dissolved in THF (35 ml) and added rapidly dropwise. The reaction mixture was stirred at 0° C. for one hour. A THF-water mixture (1:1 v/v 6 ml) was added slowly followed by 10% sodium hydroxide (10 ml). The mixture was filtered and the residue washed well with ethyl acetate. The combined filtrate was dried over anhydrous potassium carbonate and evaporated to an oil (3.5 g) which was converted to the hydrochloride salt using 4N isopropanolic HCl.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6,9; N, 3.86. Found: C, 52.71; H, 6.63; N, 3.71.

NMR Analysis: (DMSO): δ 7.4 (4H, aromatic) 3.55 (2H doublet CH—$CH_2N(CH_3)_2$); 3.05 (1H, triplet, CH—$CH_2N(CH_3)_2$); 2.63 (6H singlet, N—$(CH_3)_2$) 1.30 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 16

1-[1-(3-bromophenyl)-2-dimethylamino)ethyl]cylohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-bromophenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 198°-201° C.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6.90; N, 3,86. Found: C, 52.84; H, 6.92; N, 3.99.

EXAMPLE 17

1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 214°-216° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.07; H, 7.79; N, 3.93.

EXAMPLE 18

1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of o-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 205°-206° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.45; H, 7.71; N, 4.79.

EXAMPLE 19

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dichlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 241°-244° C.

Analysis for: $C_{16}H_{23}NOCl_2.HCl$: Calculated: C, 54.47; H, 6.81; N, 3.97. Found: C, 54.8; H, 6.83; N, 3.99.

EXAMPLE 20

1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol

The product of the preceding example is similarly produced by the following procedure:

Lithium diisopropylamide was prepared by dissolving di-isopropylamine (69 ml) in THF (500 ml) followed by the addition of n-butyllithium (325 ml). After 10 minutes stirring, the straw colored liquid was cooled to −78° C. and a solution of the 3,4-dichloro-N,N-dimethylbenzeneacetamide (110.9 g, crude) was dissolved in 300 ml THF and added slowly. A dark red slurry was obtained. The mixture was stirred for a further 20 minutes and cyclohexanone (55.7 ml) was added. After 60 minutes at −78° C. the reaction mixture was poured into a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organic solution was washed with brine, dried over K_2CO_3 and evaporated. The product, 1-[(3,4-dichlorophenyl) (dimethylaminocarbonyl)methyl]cyclohexanol, crystallized and was filtered. The crystals were washed with isopropanol and with petroleum ether and air dried. Yield: 73.6 g., m.p. 118°-120° C.

To an ice cold solution of Borane THF complex (152 ml, 152 mmole) was added a solution of 1-[(3,4-dichlorophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol (30 g, 90 mmole) in THF. The mixture was refluxed for 2 hours and cooled again in an ice bath. 2N HCl (23 ml) was added and the mixture refluxed for 1.5 hours. It was cooled overnight. The reaction mixture was basified to pH 14 with solid potassium hydroxide and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to a solid. This was filtered and washed with diethyl ether and air dried. Yield: 15.4 g.; m.p. 128°-130° C.

This product was converted to the hydrochloride which was identical with the product in Example 19.

EXAMPLE 21

1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-methoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 166°-168° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.11; H, 8.68; N, 4.67. Found: C, 63.12; H, 8.54; N, 4.46.

EXAMPLE 22

1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]-cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dimethoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride.

Analysis for: $C_{18}H_{29}NO_3.HCl$: Calculated: C, 62.88; H, 8.74; N, 4.08. Found: C, 62.42; H, 8.56; N, 3.98.

EXAMPLE 23

1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4trifluoromethylphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 238°-240° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.47; H, 7.16; N, 4.07.

EXAMPLE 24

1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol was produced as the hydrochloride, m.p. 194°-196° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.31; H, 7.09; N, 4.09.

EXAMPLE 25

1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-methylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol was produced as the hydrochloride.

Analysis for: $C_{17}H_{17}NO.HCl$: Calculated: C, 68.54; H, 9.17; N, 4.70. Found: C, 68.37; H, 9.31; N, 4.83.

EXAMPLE 26

1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(4-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product to remove the benzyl protecting group from the 4-hydroxyphenyl moiety was accomplished by dissolving 1.0 grams of the product in 100 ml. ethanol. One gram, 10% Pd/C was introduced followed by cyclohexa-1,4-dienone (5 ml.). The mixture was stirred for ninety minutes at ambient temperature. The catalyst was removed by filtration and the solvent removed by evaporation to yield 800 mg. of solid. This solid 4-hydroxyphenyl product was converted to its fumarate salt via an acetone-ethanol solution, m.p. 140°-142° C.

Analysis for: $C_{16}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 63.30; H, 7.70; N, 3.69. Found: C, 62.18; H, 7.90; N, 3.63.

EXAMPLE 27

1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(3-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product (2.3 g) was conducted in 200 ml ethanol employing a Paar bomb, 300 mg. 10% Pd/C until uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent evaporated to afford a solid product which was converted to its hydrochloride salt with 5N isopropanolic hydrochloride, m.p. 162°-164° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.08; H, 8.74; N, 4.67. Found: C, 62.78; H, 8.55; N, 4.55.

EXAMPLE 28

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol

By replacing cyclohexanone in Example 14 with a molar equivalent amount of cyclobutanone and following the procedure described in Example 15, 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol was obtained. It was converted to the hydrochloride salt, m.p. 220°-222° C.

Analysis for: $C_{14}H_{20}NOBr.HCl$: Calculated: C, 50.22; H, 6.28; N, 4.19. Found: C, 50.26; H, 6.11; N, 4.13.

EXAMPLE 29

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol

By replacing p-bromophenylacetic acid with a molar equivalent amount of p-methoxyphenyl acetic acid in Example 13, 4-methoxy-N,N-dimethylbenzene acetamide was obtained. Subsequently, following the procedure outlined in Example 14, replacing cyclohexanone with a molar equivalent amount of cyclopentanone, there was obtained the corresponding cyclopentanol derivative. This intermediate was converted, following the procedure described in Example 15, to the title compound as the hydrochloride, m.p. 194° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.07; H, 8.76; N, 4.67. Found: C, 64.19; H, 8.72; N, 4.33.

EXAMPLE 30

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol

By replacing cyclopentanone with a molar equivalent of cycloheptanone in Example 27, the title compound was obtained as the hydrochloride, m.p. 175°-177° C.

Analysis for: $C_{18}H_{29}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.03; H, 9.26; N, 4.21. Found: C, 65.25; H, 9.16; N, 4.29.

EXAMPLE 31

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol

By replacing cyclopentanone with a molar equivalent amount of cyclooctanone in Example 29, the title compound was obtained as the hydrochloride, m.p. 178°-180° C.

Analysis for: $C_{19}H_{31}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.87; H, 9.48; N, 4.04. Found: C, 65.79; H, 9.08; N, 3.95.

EXAMPLE 32

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol

By replacing 4-bromo-N,N-dimethylbenzeneacetamide with a molar equivalent of 4-methoxy-N,N-dimethylbenzeneacetamide in Example 14, and cyclohexanone with 2-cyclohexen-1-one, was obtained the corresponding cyclohexenone derivative. This intermediate was converted following the procedure described in Example 15 to the title compound as the fumarate, m.p. 128°-130° C.

Analysis for: $C_{17}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 64.4; H, 7.31; N, 3.58. Found: C, 63.8; H, 7.46; N, 3.88.

EXAMPLE 33

Resolution of Racemic 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (48.0 g., 0.173 m) dissolved in ethyl acetate (350 ml) was treated with di-p-toluoyl-d-tartaric acid (33.5 g., 0.082 m) dissolved in ethyl acetate (250 ml). After standing overnight, the solid was filtered. The solid was recrystallized three times by dissolving in boiling ethyl acetate (300 ml) and methanol (50 ml), concentrating by boiling to incipient crystallization and chilling. Yield 31.7 g., m.p. 126°-128° C. $[\alpha]_D^{25} = -50.51$; c = 1.03 ethanol.

The salt was converted to its free base by shaking in 2N sodium hydroxide and diethyl ether. The ether layer was washed with brine, dried over anhydrous sodium carbonate, evaporated and dried in vacuo. yield 16.4 g., 68.5%. m.p. 104°-5° C. $[\alpha]_D^{25} = +27.95$; c = 1.15, 95% ethanol.

The base was dissolved in ether (500 ml) and treated with 4.5N hydrogen chloride in isopropanol (20 ml). The resulting hydrochloride salt was recrystallized from warm methanol (75 ml) by dilution with ether (400 ml) and chilling. Yield 16.6 g. m.p. 239°-241° C. $[\alpha]_D^{25} = -4.38$; c = 1.01, 95% ethanol.

The filtrate and washings from the original di-p-toluoyl-d-tartrate salt were evaporated to dryness. The free base was obtained by shaking the solid with 2N sodium hydroxide (400 ml), extracting with diethyl ether

(3×250 ml), washing the extracts with brine and drying. Yield 24.2 g. The base was dissolved in ethyl acetate (150 ml) and treated with di-p-toluoyl-l-tartaric acid (16.75 g, 0.0435 m) dissolved in ethyl acetate (150 ml). After standing overnight the salt was filtered and was recrystallized twice from ethyl acetate (300 ml) and methanol (50 ml) as described. Yield 29.4 g. m.p. 124°-127° C. $[\alpha]_D^{25} = +50.77$, c=0.845 ethanol.

The base was obtained in the manner described. Yield 14.7 g. m.p. 104°-105° C. $[\alpha]_D^{25} = -26.56$, c=1.22%, 95% ethanol.

The free base was converted to the hydrochloride salt. Yield 14.5 g. m.p. 239°-241° C. $[\alpha]_D^{25} = +4.98$, c=1.01, 95% ethanol.

EXAMPLE 34

1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol

17.0 g (0.095 moles) of p-aminophenylacetic acid, dimethylamide was dissolved in 500 ml of tetrahydrofuran, placed under a nitrogen atmosphere, and cooled to −20° C. 23.6 g (1.15 equivalents) of 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene was added, followed dropwise by a solution of 42 g (2.4 equivalents) of sodium bis(trimethylsilyl)amide in 250 ml of THF. The mixture was allowed to warm to room temperature and was stirred for 18 hours.

The mixture was next cooled to −78° C. and 71.6 ml (1.2 equivalents) of 1.6N n-butyl lithium in hexane added. The reaction was stirred for 45 minutes and then 20 ml (2.0 equivalents) of cyclohexanone added. The mixture was stirred for an additional 1 hour at −78° C. and then poured into a saturated aqueous solution of ammonium chloride. The organic phase was removed and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo to yield 20 g of crude 1-[(4-aminophenyl)(dimethylaminocarbonyl)-methyl]cyclohexanol. Column chromatography on silica gel with 1% methanol in methylene chloride gave 16 g of essentially pure white solid. A sample twice recrystallized from ethanol had m.p. 169°-170° C. and the following elemental analysis:

Analysis for: $C_{16}H_{24}O_2N_2$: Calculated: C, 69.51; H, 8.77; N, 10.14. Found: C, 69.69; H, 8.96; N, 10.26.

5.0 g (0.018 mole) of the above amide was dissolved in 300 ml of dry tetrahydrofuran and added dropwise to a mixture of 1.1 g of lithium aluminum hydride and 8.0 ml of concentrated sulfuric acid in 200 ml of tetrahydrofuran at 0° C. The mixture was stirred at 0° C. for five hours, then the excess reagent was destroyed by the dropwise addition of 4 ml of 50:50 THF-water, then 4 ml of 15% aqueous sodium hydroxide and finally 4 ml of water. The mixture was filtered and the precipitate washed several times with THF. The combined filtrates were evaporated and the residue recrystallized from isopropanol to give 3.8 g of the title compound as the free base. Treatment with excess oxalic acid in ethyl acetate gave the dioxalate, m.p. 105° C.(d).

Analysis for: $C_{20}H_{30}N_2O_9$: Calculated: C, 54.28; H, 6.84; N, 6.33. Found: C, 53.96; H, 6.83; N, 6.24.

EXAMPLE 35

1-[1-(4-nitrophenyl)-2-dimethylaminoethyl]cyclohexanol

2.0 g (7.6 mmoles) of 1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 50 ml of methylene chloride and added dropwise to a stirring solution of 2.2 g (2.5 equivalents) of nitrosonium tetrafluoroborate. The reaction was stirred at room temperature for four hours. The methylene chloride was then removed in vacuo and replaced with 100 ml of water. This solution was added slowly to a mixture of 2.0 g of copper in 200 ml of 1N sodium nitrite and the combination stirred for 2 hours at room temperature. Extraction with methylene chloride, drying, and evaporation in vacuo yielded 2.0 g of the free base of the title compound. Recrystallization from isopropanolic HCl gave the hydrochloride, m.p. 211°-212° C.

Analysis for: $C_{16}H_{24}O_3N_2$: Calculated: C, 58.42; H, 7.37; N, 8.52. Found: C, 58.03; H, 7.53; N, 8.69.

EXAMPLE 36

1-[2-dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol

By replacing 1-[2-amino-1-(p-methoxyphenyl)ethyl]-cyclohexanol in Example 3 with a molar equivalent amount of 1-[2-amino-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol and refluxing overnight, the title compound was obtained, m.p. 218°-220° C.

Analysis for: $C_{17}H_{26}NO_2Br.HCl$: Calculated: C, 57.98; H, 6.92; N, 3.56. Found: C, 51.57; H, 6.79; N, 3.46.

EXAMPLE 37

1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]-]cyclohexanol

14.7 g (0.10 mole) of p-methoxyphenylacetonitrile was dissolved in 250 ml of dry tetrahyrofuran and placed in a dry ice/isopropanol bath under N_2. 69.0 ml of 1.6M n-butyl lithium (0.11 mole) was added dropwise over 30 minutes and the mixture stirred at −78° C. for one hour. The lithium salt of the nitrile precipitated as a yellow solid during this time. 71.0 g (0.50 mole) of methyl iodide was then added and stirring at −78° C. continued for an additional hour. The mixture was then poured into saturated ammonium chloride and the product extracted into diethyl ether, washed with saturated sodium chloride and dried over sodium sulfide. It was filtered and evaporated, redissolved in methylene chloride and passed through Florisel®. Evaporation gave 15.0 g of α-(p-methoxyphenyl)propionitrile as an orange oil.

The α-(p-methoxyphenyl)propionitrile prepared above was redissolved in 250 ml of tetrahydrofuran and cooled to −78° C. in dry ice/isopropanol. 69.0 ml of 1.6M n-butyllithium was added over 30 minutes and the mixture stirred for 1 hour under nitrogen. 20 ml of cyclohexanone was then added and stirring at 078° C. was continued for an additional hour. The mixture was poured into saturated ammonium chloride solution and the product extracted with diethyl ether. It was washed with water, saturated sodium chloride and dried over sodium sulfate. Filtration and evaporation gave 21.5 g of white solid. A sample twice recrystallized from benzene had m.p. 129° C. and the following analysis:

Analysis for: $C_{16}H_{21}NO_2$: Calculated: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.95; H, 8.04; N, 5.29.

4.0 g (15 mmoles) of the β-hydroxynitrile prepared above was dissolved in 200 ml of tetrahydrofuran and 50 ml of 1M borane tetrahydrofuran complex was added. The mixture was refluxed for 2 hours and allowed to cool. 200 ml of 2N HCl was added and the THF removed in vacuo. The aqueous solution was made basic by the addition of solid pottasium carbonate

and the product extracted with 500 ml of ethyl acetate, washed with saturated sodium chloride and dried over sodium sulfate. This was filtered and evaporated and treated with isopropanolic HCl and diethyl ether to yield 3.3 g of the primary amine, m.p. 209° C.

Analysis for: $C_{16}H_{26}NO_2Cl$: Calculated: C, 64.09; H, 8.74; N, 4.67. Found: C, 63.70; H, 8.60; N, 4.59.

3.0 g (10 mmole) of the primary amine hydrochloride was dissolved in 200 ml of absolute ethanol. 5.0 ml of 37% aqueous formaldehyde and 1.0 g of 10% palladium on carbon were added and the mixture was treated with 50 psi of hydrogen on a Parr shaker for 3 days. The mixture was then filtered and evaporated and the solvent replaced with 300 ml of water and washed with 300 ml of ethyl acetate. The aqueous solution was then made pasic with solid sodium carbonate and again extracted with ethyl acetate. The organic extract was washed with saturated brine and dried over sodium sulfate. It was filtered and evaporated and the title compound precipitated as the hydrochloride from isopropanol/ether by the addition of isopropanolic HCl. A second crystallization from isopropanol gave 2.0 g of white solid, m.p. 271° C.

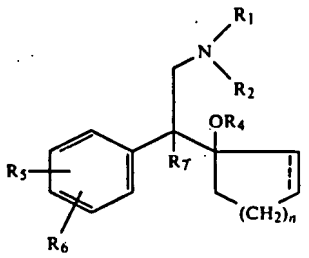
Analysis for: $C_{18}H_{30}NO_2Cl$: Calculated: C, 65.93; H, 9.22; N, 4.27. Found: C, 65.73; H, 8.93; N, 4.20.

EXAMPLE 38

By following a procedure similar to Examples 13 to 15, using (a) 3,4-dibromophenylacetic acid, (b) 3-methylphenylacetic acid, (c) 4-bromophenylacetic acid and (d) 3-methoxyphenylacetic acid instead of p-bromophenylacetic acid and, as the cycloalkanone, (a) cyclohexanone, (b) cyclohexanone, (c) cyclobutanone and (d) cyclopentanone, there are prepared (a) 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol, (b) 1-[2-(dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol, (c) 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol and (d) 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol.

What is claimed is:

1. A compound of the formula:



wherein

the dotted line represents optional olefinic unsaturation, and

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 in which in which R_1 is hydrogen or alkyl of 1 to 3 carbon atoms; R_2 is alkyl of 1 to 3 carbon atoms; R_5 is hydrogen, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms; R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms; R_7 is hydrogen or alkyl of 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2 in which R_5 and R_6 are in meta or para positions and n is 2.

4. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is 1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 which is 1-(α-[methylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 which is 1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 which is 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 which is 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1 which is 1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1 which is 1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]]cyclohexanol or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 which is 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 which is 1-[1-(4-aminophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1 which is 1-[1-(4-nitrophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1 which is 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclobutanol or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000229

AMERICAN HOME PRODUCTS CORPORATION
ATTN: RONALD W. ALICE
685 THIRD AVENUE- PATENT DEPT. 15TH FL.
NEW YORK, NY 10017

DATE MAILED
01/19/93

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	S
1	4,535,186	184	1870	----	06/545,701	08/13/85	10/26/83	08	NO	P

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	AHP-8162-2C

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

EXHIBIT II

MAJOR NUMBER
000125

AMERICAN HOME PRODUCTS CORPORATION
PATENT DEPT. - 25TH FLOOR
685 THIRD AVENUE
NEW YORK, NY 10017

DATE MAILED

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,533,551	173	450	----	06/581,448	08/06/85	02/17/84	04	NO	PAID
2	4,533,926	173	450	----	06/452,538	08/06/85	12/23/82	04	NO	PAID
3	4,537,196	170	225	----	06/333,088	08/27/85	12/21/81	04	NO	PAID
4	4,535,168	173	450	----	06/463,430	08/13/85	02/03/83	04	NO	PAID
5	4,535,186	173	450	----	06/545,701	08/13/85	10/26/83	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	AHP-8451
2	AHP-8205
3	AHP-7326
4	AHP-8[illegible]
5	AHP-8[illegible]

DIRECT THE COMMISSIONER OF

QUESTIONS ABOUT THIS NOTICE TO:
MARKS, BOX M. FEE, WASHINGTON, DC 20231

EXHIBIT III

REGULATORY CHRONOLOGY FOR
IND NO. 27,323

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
October 22, 1985	IND submitted.
October 24, 1985	FDA letter acknowledges receipt of our IND and assigns IND #27,323 to WY-45,030 HCl.
November 26, 1985	Correspondence to Dr. Leber providing the test specifications, methods and the solubility profile of specific batches of raw materials used in the synthesis of WY-45,030 HCl.
January 23, 1986	Protocol amendment for a new protocol, 600A-101-US.
January 27, 1986	FDA letter requesting responses to chemistry, clinical and preclinical deficiencies noted in our original IND submission.
May 1, 1986	Protocol amendment for a new protocol, 600A-201-US.
May 1, 1986	Protocol amendment for a new protocol, 600A-202-US.
May 12, 1986	Submission to Dr. Leber providing responses to inquiries noted in FDA's letter dated January 27, 1986.
October 24, 1986	IND Annual Report.
November 24, 1986	Information amendment: CMC adding a new tablet strength (100 mg) for use in clinical trials.
January 7, 1987	Information amendment: CMC amending the impurity limits for WY-45,821, an intermediate in the synthesis of WY-45,030 HCl.
January 15, 1987	Protocol amendment for a new protocol, 600A-203-US.
January 29, 1987	Correspondence to Dr. Leber requesting comments on our plans to address several "Investigational Concerns" regarding our Phase 2 and 3 clinical trials.
March 11, 1987	Protocol amendment for a new protocol, 600A-204-US.
March 13, 1987	FDA letter providing a response to our correspondence of January 29, 1987.
April 24, 1987	Information amendment: CMC providing for the manufacture and use of a deuterated form of WY-45,030.
June 9, 1987	Information amendment: CMC providing for the use of an alternate method of synthesis for WY-45,030 HCl.
June 23, 1987	Correspondence to Dr. Leber documenting a conference call held between Dr. Laughren and Wyeth-Ayerst representatives regarding the clinical development of WY-45,030 HCl.
July 17, 1987	Correspondence to Dr. Leber requesting permission to continue treatment beyond the initial 7-week duration for a patient enrolled in trial 600A-203-US.

REGULATORY CHRONOLOGY FOR
IND NO. 27,323

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
July 24, 1987	FDA letter providing responses to questions raised during a June 5, 1987 teleconference regarding ophthalmologic exams, extension studies of individual patients, and the minimum requirements for long-term safety data.
August 4, 1987	Correspondence to Dr. Leber documenting the July 20, 1987 telephone contact, in response to our letter of July 17, 1987, in which FDA granted permission for a patient to continue treatment beyond the initial 7-week duration of trial 600A-203.
November 24, 1987	IND Annual Report.
December 11, 1987	Information amendment: CMC providing for the use of an alternate method of synthesis for WY-45,030 HCl.
December 16, 1987	Correspondence to Dr. Leber requesting Division input regarding the acceptability of methods used to collect long-term safety data based on ophthalmological examinations.
January 18, 1988	Correspondence to Dr. Leber requesting an End-of-Phase 2 conference.
January 26, 1988	Submission to Dr. Leber providing preliminary evidence of the safety and efficacy of venlafaxine compared to placebo and requesting permission to enroll women of childbearing potential into our Phase 2 clinical program.
March 4, 1988	Information amendment: CMC providing for the use of colorants and an improved assay method for the drug product, revised test methods and specifications for the drug substance, and information pertaining to the manufacture and control of placebo dosage forms.
March 14, 1988	Submission to Dr. Leber providing an interim statistical analysis to support preliminary proof of efficacy, as requested by Dr. Kapit, Medical Review Officer.
April 12, 1988	End-of-Phase 2 conference.
April 15, 1988	Protocol amendment for two new protocols, 600A-301-US and 600A-303-US.
April 19, 1988	Letter from FDA granting Wyeth-Ayerst permission to enroll women of childbearing potential in venlafaxine studies and to enroll patients into long-term protocols.
April 25, 1988	Submission providing a report concerning the preliminary results of the metabolic disposition of venlafaxine HCl in man, as requested by Dr. G. Evoniuk, Reviewing Pharmacologist.
May 12, 1988	Protocol amendment for three new protocols: 600A-300-US, 600A-305-US and 600A-307-US.
May 13, 1988	Letter from FDA requesting that an additional laboratory evaluation take place at the two-week study point in our phase 3 protocols.
June 6, 1988	Protocol amendment for a new protocol, 600A-302-US.

REGULATORY CHRONOLOGY FOR
IND NO. 27,323

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
June 22, 1988	Protocol amendment for two new protocols: 600A-304-US and 600A-306-US.
July 12, 1988	Protocol amendment for a new protocol, 600A-312-US.
August 3, 1988	Information amendment: CMC updating IND No. 27,323 in response to issues raised during the End-of-Phase 2 conference.
August 10, 1988	Protocol amendment for a new protocol, 600A-310-US.
September 6, 1988	Protocol amendment for a new protocol, 600A-302-CA.
September 23, 1988	Information amendment: CMC providing responses to comments expressed at the End-of-Phase 2 conference regarding the description of the drug substance synthesis and investigational labeling.
October 4, 1988	Protocol amendment for two new protocols: 600A-109-US and 600A-110-US.
October 27, 1988	Protocol amendment for a new protocol, 600A-111-US.
November 9, 1988	Correspondence to Dr. Leber requesting comment on a proposed stability protocol for venlafaxine tablets.
January 9, 1989	Correspondence to Dr. Leber documenting an agreement between Wyeth-Ayerst and FDA representative Mr. Tony DeCicco stating it is acceptable for future clinical trials not to provide for a two-week laboratory evaluation.
February 22, 1989	Protocol amendment for a new protocol, 600A-113-US.
February 23, 1989	Submission notifying FDA that Wyeth-Ayerst had discontinued Protocol 600A-110-US due to an insufficient number of qualified subjects who could meet the selection criteria for "hepatically-impaired patients" as identified in the protocol.
February 24, 1989	Protocol amendment for a new protocol, 600A-323-US.
March 21, 1989	IND Annual Report.
May 3, 1989	Protocol amendment for two new protocols: 600A-313-US and 600A-314-US.
May 10, 1989	Submission providing data requested by Dr. Evoniuk, Pharmacology Reviewer, during the venlafaxine End-of-Phase 2 conference regarding our Segment II rabbit and Segment I and II rat studies.
June 15, 1989	Protocol amendment for a new protocol, 600A-121-US.
July 18, 1989	FDA letter reconfirming permission to treat patients in long-term extension protocols and requesting additional information for the CMC section of the IND.
August 4, 1989	Information amendment: CMC to add a new site of tablet manufacturing and a new site for packaging.

REGULATORY CHRONOLOGY FOR
IND NO. 27,323

EFFEXOR™ (VENLAFAXINE·HCl; WY-45,030)

DATE	COMMENTS
October 20, 1989	Information amendment: CMC to include a new dosage form and a protocol amendment for a new protocol, 600A-120-US.
October 23, 1989	Protocol amendment for two new protocols: 600A-300-CA and 600A-304-CA.
November 3, 1989	IND Annual Report.
November 29, 1989	Protocol amendment for a new protocol, 600A-116-US.
December 20, 1989	Protocol amendment for a new protocol, 600A-114-US.
January 16, 1990	Protocol amendment for a new protocol, 600A-117-US.
January 19, 1990	Protocol amendment for a new protocol, 600A-330-US.
February 14, 1990	FDA letter citing deficiencies in our information amendment: CMC dated October 20, 1989 regarding analytical methods used in the identification of venlafaxine HCl drug substance.
March 13, 1990	Response to FDA's comments in their letter dated July 18, 1989 regarding additional CMC and preclinical pharmacology information.
April 17, 1990	Protocol amendment for a new protocol, 600A-123-US.
May 3, 1990	Submission responding to the CMC comments made in FDA's letter of February 14, 1990.
July 6, 1990	FDA letter providing comments on Protocol 600A-123-US, submitted on April 17, 1990.
July 27, 1990	FDA letter requesting clarification of the CMC section of our submissions dated August 4, 1989 and May 3, 1990.
August 31, 1990	Protocol amendment for a new protocol, 600A-328-US.
September 10, 1990	Protocol amendment for a new protocol, 600A-327-US.
September 11, 1990	Submission to Dr. Leber responding to comments made in FDA's letter of July 6, 1990 regarding protocol 600A-123-US.
October 16, 1990	Protocol amendment for a new protocol, 600A-332-US.
November 5, 1990	Response to FDA's letter dated July 27, 1990 regarding our information amendments: CMC submitted on August 4, 1989 and May 3, 1990.
January 30, 1991	IND Annual Report.
March 6, 1991	Protocol amendment for a new protocol, 600A-124-US.
March 11, 1991	Protocol amendment for a new protocol, 600A-343-US.
April 25, 1991	NDA filed.
August 12, 1991	Submission to Mr. Young, Clinical Investigations Branch, providing information regarding the inspection of investigational sites involved in the clinical trials designed to establish efficacy and safety of venlafaxine.
October 31, 1991	IND Annual Report.

REGULATORY CHRONOLOGY FOR
IND NO. 27,323

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
May 5, 1992	Protocol amendment for a new protocol, 600A-125-US.
May 7, 1992	Information amendment: CMC to reflect the specifications and analytical methods described in our pending NDA.
November 11, 1992	IND Annual Report.
December 21, 1993	IND Annual Report.

REGULATORY CHRONOLOGY FOR
NDA No. 20-151

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
April 25, 1991	NDA for venlafaxine hydrochloride submitted.
April 26, 1991	NDA for venlafaxine hydrochloride received by FDA.
June 18, 1991	FDA letter to Mr. Justin Victoria acknowledges receipt of our NDA, assigns number 20-151 to the NDA, and informs us that the filing date will be June 26, 1991.
June 26, 1991	NDA filing date (as noted in FDA's June 18, 1991 letter).
August 12, 1991	Correspondence to Dr. Robert Young in response to his telephone request of July 30, 1991 to provide a copy of Phase 2 and 3 clinical protocols and information regarding the investigators that participated in these studies.
October 28, 1991	FDA letter provides a summary of the deficiencies noted in the Chemistry, Manufacturing and Controls (CMC) section of NDA 20-151.
December 12, 1991	Submission to Dr. Leber providing our responses to CMC deficiencies described in FDA letter dated October 28, 1991.
January 15, 1992	FDA letter acknowledges receipt of our responses to the CMC deficiencies noted in FDA letter dated October 28, 1991.
January 16, 1992	Submission to Dr. Leber which includes the results of a bioequivalence trial for a new venlafaxine 100 mg tablet versus 4 x 25 mg tablets.
March 4, 1992	Correspondence to Dr. Leber in response to the February 24, 1992 telephone request by Dr. James Knudsen to provide the number of subjects/patients exposed to venlafaxine during clinical investigations and demographic data of the study population.
March 6, 1992	Correspondence to Dr. Leber in response to the March 5, 1992 telephone request by Dr. James Knudsen to verify the number of patients exposed to venlafaxine.
March 13, 1992	Correspondence to Dr. Leber in response to the March 11, 1992 telephone request by Dr. James Knudsen for additional demographic information with respect to our clinical trials.
April 3, 1992	Correspondence to Dr. Leber in response to a telephone request from Dr. James Knudsen for descriptions of information about the safety data base in our NDA 20-151.
April 13, 1992	Correspondence to Dr. Leber in response to the April 8, 1992 request from Dr. James Knudsen for a statistical comparison of adverse experience incidence in 4-to-6 week, placebo-controlled clinical trials.

REGULATORY CHRONOLOGY FOR
NDA No. 20-151

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
May 4, 1992	Correspondence to Dr. Leber in response to the April 30, 1992 request by Dr. James Knudsen for information regarding study events, seizure experience and withdrawal phenomenon.
May 8, 1992	Submission to Dr. Robert Young providing case report forms for several patients.
May 26, 1992	Correspondence to Dr. Leber in response to a telephone request from Dr. James Knudsen for an analysis of suicide attempts in clinical trials and subgrouping of suicide attempts by overdose.
July 22, 1992	Correspondence to Dr. Leber in response to the July 20, 1992 telephone request by Dr. Hillary Lee for demographic information regarding race.
July 29, 1992	Correspondence to Dr. Leber providing the Safety Update which amends the Integrated Summary of Safety (ISS) contained in our April 25, 1991 NDA submission.
August 27, 1992	Correspondence to Dr. Leber in response to the August 20, 1992 telephone request from Dr. Hillary Lee to provide comparative data on the mean baseline values for the HAM-D Total, Depressed Mood (Item #1), MADRS Total and CGI-Severity rating scales for the pivotal Phase 2 and 3 clinical trials.
October 14, 1992	FDA telefax from Dr. James Knudsen requesting the completion of summary tables as provided by FDA.
October 19, 1992	Correspondence to Dr. Leber in response to telephone requests from Drs. James Knudsen and Hillary Lee on September 10, 14 and 18, 1992 concerning the medical/clinical review of NDA 20-151.
October 21, 1992	Correspondence to Dr. Leber in response to a telephone request from Dr. James Gebert concerning extrapolated data points for the HAM-D rating scale.
October 23, 1992	Correspondence to Dr. James Gebert providing a list of patient numbers by investigator and subinvestigator.
October 23, 1992	Correspondence to Dr. Leber responding to Dr. Hillary Lee's telephone request to provide updated efficacy tables.
October 26, 1992	FDA telefax from Dr. Hillary Lee requesting clarification of our definition of "intent-to-treat population."
October 27, 1992	FDA letter requesting a copy of the procedure utilized in the analysis of the HAM-D totals in 2 Protocols.
November 6, 1992	Correspondence to Dr. Leber regarding questions received from Dr. James Gebert concerning p-values contained in our investigator-by-treatment interaction tables.

REGULATORY CHRONOLOGY FOR
NDA No. 20-151

EFFEXOR™ (VENLAFAXINE HCl; WY-45,030)

DATE	COMMENTS
November 11, 1992	Correspondence to Dr. Leber providing additional safety tables as requested by Dr. James Knudsen on October 13, 1992 and additional demographic tables as requested by Dr. Hillary Lee on October 21, 1992.
December 1, 1992	Correspondence to Dr. Leber in response to questions from Dr. James Gebert regarding the reanalysis of various efficacy parameters in 3 protocols.
December 8, 1992	FDA letter from Dr. Leber comments on our definition of intent-to-treat and requests a list, for each study, of patients who were excluded from our intent-to-treat analyses.
December 22, 1992	Correspondence to Dr. Leber responding to a December 17, 1992 request by Dr. Hillary Lee to conduct an analysis of variance (ANOVA) for the CGI scores in several Protocols.
January 7, 1993	Correspondence to Dr. Leber in response to FDA letter of December 8, 1992 concerning intent-to-treat analysis.
January 20, 1993	Correspondence to Dr. Leber in response to questions from Drs. Hillary Lee and James Gebert dated December 8, 1992 to provide a reanalysis of intent-to-treat patients from study 600A-203.
January 21, 1993	FDA telefax from Dr. Thomas Laughren requested patient exposure data (PEY) for the Phase 2-3 studies and clarification of the cutoff date for deaths and reportable study events in our Safety Update of July 29, 1992.
January 22, 1993	FDA telefax from Dr. Thomas Laughren requested additional information on deaths provided in our Safety Update of July 29, 1992 and the death and serious event tables provided in our amendment of October 19, 1992.
January 26, 1993	Correspondence to Dr. Leber responding to telefaxes from Dr. Laughren dated January 21 and 22, 1993 regarding safety tables presented in our July 29, 1992 Safety Update.
January 28, 1993	FDA telefax from Dr. Thomas Laughren requested information regarding adverse event data.
January 28, 1993	FDA telefax from Dr. Thomas Laughren requested information regarding criteria for laboratory abnormalities, statistical testing of samples and patient withdrawal due to laboratory abnormalities.
January 29, 1993	FDA telefax from Dr. Thomas Laughren requested information concerning vital signs and weight change data regarding statistical testing and patient withdrawal due to vital sign and weight change abnormalities.
February 2, 1993	Correspondence to Dr. Leber responding to telefaxes from Dr. Laughren dated January 21, 22, 26, 28 (two faxes) and 29, 1993 for additional information concerning safety issues and laboratory, vital sign and weight change data.

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DATE	COMMENTS
February 4, 1993	FDA telefax from Dr. James Knudsen requested a table of patients who discontinued due to hypertension/high blood pressure.
February 8, 1993	FDA telefax from Mr. Paul David requested efficacy analysis by sex for the HAM-D depression item, CGI severity score and MADRS total score for several Phase 2 and 3 Protocols.
February 9, 1993	FDA telefax by Dr. Thomas Laughren requested a clarification of the adverse effect data listed in a table contained in our February 2, 1993 correspondence.
February 9, 1993	Correspondence to Dr. Leber providing various study event and patient discontinuation information in response to requests from Drs. James Knudsen and Thomas Laughren on February 2, 4, and 5, 1993.
February 10, 1993	FDA telefax from Dr. James Knudsen requested information regarding patient discontinuations due to laboratory test abnormalities.
February 10, 1993	FDA telefax from Dr. Thomas Laughren requested information regarding the results of statistical testing of laboratory data and confirmation of the number of patient withdrawals due to laboratory abnormalities.
February 18, 1993	Correspondence to Dr. Leber responding to the February 10, 1993 request from Dr. Thomas Laughren regarding laboratory data.
February 19, 1993	Correspondence to Dr. Leber providing a table of the incidence of patient discontinuations for laboratory test abnormalities, as requested by Dr. James Knudsen on February 10, 1993.
February 22, 1993	Correspondence to Dr. Leber in response to a February 9, 1993 request by Dr. Thomas Laughren to provide information regarding adverse events.
February 23, 1993	FDA telefax from Dr. Thomas Laughren requesting trend tests.
February 24, 1993	Correspondence to Dr. Leber responding to the January 28, 1993 telefax from Dr. Laughren requesting adverse event data.
February 26, 1993	Correspondence to Dr. Leber responding to the February 8, 1993 telefax from Mr. Paul David requesting a subgroup analysis by sex.
March 1, 1993	Submission to Dr. Leber providing batch number, size and date of manufacture for drug product as requested by Dr. Safaa Abraham, Division of Biopharmaceutics.
March 3, 1993	FDA telefax from Dr. Laughren requesting an assessment of findings of syncope in a total of 5 patients.
March 5, 1993	FDA telefax from Dr. Laughren requested information regarding the predictability of demographic variables on adverse events.

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DATE	COMMENTS
March 8, 1993	Correspondence to Dr. Leber summarizing the teleconference held on February 18, 1993 regarding biopharmaceutic data and providing responses to questions raised at this teleconference.
March 9, 1993	Correspondence to Dr. Leber responding to the March 3, 1993 telefax from Dr. Laughren regarding a total of 5 patients characterized as having syncope.
March 10, 1993	Correspondence to Dr. Leber providing additional biopharmaceutical information in response to our teleconference of February 18, 1993.
March 10, 1993	Submission to Dr. Leber providing the results of a pharmacokinetic study of venlafaxine when administered b.i.d. and CMC information for a 37.5 mg tablet.
March 11, 1993	FDA telefax from Dr. Laughren indicating the acceptability of our plan for a final Safety Update.
March 12, 1993	Correspondence to Dr. Leber in response to the March 5, 1993 request from Dr. Thomas Laughren concerning the predictive value of demographic variables in the occurrence of adverse events.
March 19, 1993	Submission to Dr. Leber providing information on the pharmacokinetic parameters and statistical comparisons of venlafaxine and O-desmethylvelafaxine.
March 24, 1993	Submission to Dr. Leber providing supplemental volumes not included in a report submitted on March 10, 1993.
March 24, 1993	Submission to Dr. Leber providing pharmacokinetic data requested on March 19, 1993 by Dr. Safaa Abraham, Division of Biopharmaceutics.
March 31, 1993	Correspondence to Dr. Leber in response to the March 23, 1993 telephone request from Dr. James Gebert for additional analysis of the mean changes from baseline for the Last Observation Carried Forward (LOCF) and Observed Cases intent-to-treat data.
April 1, 1993	Correspondence to Dr. Leber providing summary information to be used by the Psychopharmacologic Drugs Advisory Committee in preparation for our April 30, 1993 meeting.
April 16, 1993	Correspondence to Dr. Leber providing updated tables to our February 22, 1993 submission depicting the incidence of drug-related adverse events over time.
April 27, 1993	Correspondence to Dr. Leber responding to an April 23, 1993 request by Mr. Paul David to provide plasma concentrations for venlafaxine and O-desmethylvenlafaxine following administration of 375 mg/day.
May 11, 1993	Submission to Dr. Leber providing updated product labeling (dated 11 May 1993) for Effexor™ Tablets, as requested by Mr. Paul David.

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DATE	COMMENTS
May 20, 1993	Submission to Dr. Leber of NDA submission history, as requested by Mr. Paul David.
May 25, 1993	Submission to Dr. Leber responding to a request raised at the April 30, 1993 Advisory Committee meeting and discussed during a May 10, 1993 teleconference with the Division to provide analyses of blood pressure changes in patients involved in Phase 2 and 3 clinical trials.
June 1, 1993	Submission to the Division of Drug Marketing, Advertising and Communication responding to a May 28, 1993 telephone request by Dr. Heidi Marchand to provide two "coming soon" convention panels that were used at a professional meeting.
June 9, 1993	Submission to Dr. Leber providing revised copies of the blood pressure analyses submitted originally on May 25, 1993.
June 23, 1993	Submission to Dr. Leber of a follow-up report providing a characterization of the patients identified as having blood pressure changes in our submission of June 9, 1993, and proposed labeling to address possible blood pressure elevations.
July 9, 1993	Submission to Dr. Leber providing copies of draft labels for trade and sample packages of Effexor Tablets.
July 16, 1993	Submission to Dr. Leber providing a revised copy of the Environmental Assessment in response to comments received from Mr. Paul David on July 7, 1993.
July 22, 1993	Submission to Dr. Leber of additional information on reference standard used in our bioavailability studies, as provided to Dr. Ray Baweja (Division of Biopharmaceutics) on July 13, 1993.
August 6, 1993	Submission to Dr. Leber of updated NDA submission history, as requested by Mr. David.
October 6, 1993	Letter to Dr. Leber committing to conduct post-approval studies to further evaluate venlafaxine's antidepressant activity.
November 8, 1993	APPROVABLE letter received from Dr. Temple.
November 10, 1993	Letter notifying Dr. Leber of our intention to file an amendment and to pursue approval of NDA 20-151 for Effexor Tablets.
November 17, 1993	Response to several issues identified in FDA's November 8, 1993 approvable letter.
November 19, 1993	Response to three (3) of the remaining issues identified in FDA's approvable letter.
November 22, 1993	Final Safety Update submitted (remaining issue from approvable letter).
December 6, 1993	Submission to Dr. Leber providing revisions to ADVERSE REACTIONS and OVERDOSAGE sections of proposed labeling.

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DATE	COMMENTS
December 10, 1993	Submission of update NDA submission history, as requested by Mr. David.
December 10, 1993	Telefax from FDA requesting additional information for Environmental Assessment (EA).
December 13, 1993	Teleconference held with FDA to discuss issues relating to NDA approval, particularly regarding labeling.
December 15, 1993	Submission to Dr. Leber providing revised labeling for Effexor Tablets based on December 13, 1993 teleconference.
December 17, 1993	Submission to Dr. Leber providing additional information for EA in response to FDA's December 10, 1993 fax.
December 28, 1993	APPROVAL letter received (via fax) from Dr. Temple.